ACUTE TOXICITY SUMMARY

ETHYLENE GLYCOL MONOETHYL ETHER

(2-ethoxyethanol, Cellosolve)

CAS Registry Number: 110-80-5

I. Acute Toxicity Summary (for a 6-hour exposure)

Inhalation reference exposure level	**370 μg/m³**
Critical effect(s)	specific skeletal defects
Hazard Index target(s)	Reproductive/developmental

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description	colorless liquid
Molecular formula	$C_4H_{10}O_2$
Molecular weight	90.12
Density	0.931 g/cm^3 @ 20°C
Boiling point	135°C
Melting point	-70°C (solidifies)
Vapor pressure	3.8 mm Hg @ 20°C (ACGIH, 1991)
Flashpoint	44°C, closed cup
Explosive limits	upper = 15.6% lower = 1.7%
Solubility	miscible with water and organic solvents
Odor threshold	2.7 ppm (geometric mean) (AIHA, 1989)
Odor description	sweet, fruity, ester-like (AIHA, 1989)
Metabolites	ethoxyacetic acid (Groeseneken *et al*., 1986)
Conversion factor	1 ppm = 3.69 mg/m³ @ 25°C

III. Major Uses or Sources

Ethylene glycol monoethyl ether (EGEE) is used as a solvent for nitrocellulose, and natural and synthetic resins. It is used in lacquers, varnish removers, and cleaning solutions and as an antifreeze in jet fuel. EGEE is also used in the dyeing and printing of textiles.

IV. Acute Toxicity to Humans

Investigators conducting an animal experiment on the acute toxicity of EGEE intentionally exposed themselves to 6,000 ppm EGEE for “a few seconds” and reported eye irritation and a “disagreeable odor” (Waite *et al.*, 1930).

Reports of acute human toxicity following EGEE inhalation were not found in the literature. Cyanosis, pulmonary edema, and tonic-clonic spasms were reported in a woman who accidentally ingested approximately 40 ml EGEE (Reprotext, 1999).

Resting individuals exposed to EGEE retained 64% of the inhaled dose (Groeseneken *et al.*, 1986). The main metabolite of EGEE detectable in the urine of exposed persons is ethoxyacetic acid (Veulemans *et al*., 1987).

The incidence of anemia and granulocytopenia was significantly increased in shipyard painters exposed to low levels (below the TLV of 5 ppm (20 mg/m³)) of EGEE for a mean of 8 years as compared to controls (Welch and Cullen, 1988). Concomitant exposure to lead and benzene may have occurred, but the authors report that the approximate exposure levels of these toxicants during the study period were negligible.

Predisposing Conditions for EGEE Toxicity

Medical: Persons with preexisting eye, skin, kidney or blood conditions may be more sensitive (Reprotext, 1999).

Chemical: Persons with concomitant exposure to ethylene glycol or other glycol ethers may be more sensitive to the effects of EGEE exposure (Reprotext, 1999) since ethoxyacetic acid is a common metabolite among glycol ethers.

V. Acute Toxicity to Laboratory Animals

A 7-hour LC_{50} in mice of 1,820 ppm EGEE has been reported (Werner *et al*., 1943).

Four of six guinea pigs exposed to 6,000 ppm EGEE for 24-hours died; one of six guinea pigs exposed to 6,000 ppm EGEE for 8-hours died (Waite *et al*., 1930). One of six guinea pigs exposed to 1,000 ppm EGEE for either 16 or 24-hours died following exposure. Pulmonary edema, hyperemia in the kidneys, abdominal distention, and discoloration of the stomach contents were noted at necropsy of the above animals.

VI. Reproductive or Developmental Toxicity

EGEE is listed under California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a reproductive hazard.

An increased prevalence of oligospermia and azoospermia and an increased odds ratio (OR 1.85; 95% CI = 0.6-5.6) for lower sperm count were observed in a study of shipyard painters exposed to a mean of 0.8 ppm EGEE for an average of 8 years compared to unexposed workers (Welch *et al*., 1988). Lower sperm count was also reported in workers exposed to a geometric mean air concentration of 6.6 ppm EGEE for at least one month (Ratcliffe *et al*., 1989).

Exposure of male rats by gavage to 936, 1,872, and 2,808 mg EGEE/kg/day for 5 consecutive days was reported to result in reversible impairment of testicular function as indicated by significantly decreased sperm counts and increased abnormal sperm morphology (Oudiz *et al*., 1984).

Pregnant rats were exposed to 10, 50, and 250 ppm (40, 200, and 920 mg/m^3) EGEE 6 hours per day on days 6-15 of gestation (Tinston *et al*., 1983). Maternal toxicity as indicated by reduced hemoglobin, hematocrit, and mean cell volume in red blood cells was observed in rats exposed to 250 ppm EGEE. A significant reduction in the number of live fetuses was observed in rats exposed to 10 and 250 ppm, and a reduction in total litter weight was observed in rats exposed to 10 ppm and 50 ppm. Statistically significant pre-implantation loss was observed in all exposed groups and was statistically significant at 10 and 50 ppm EGEE. However, a dose-response relationship was not observed. Furthermore, since the first exposure to EGEE occurred on the expected day of implantation (gestational day 6), there was some question as to whether any increase in pre-implantation loss was exposure-related. Intergroup comparison showed significantly increased incidence of total minor skeletal defects in fetuses in the 250 ppm dose group; delayed ossification was the most common abnormality observed at this dose. Specific skeletal defects, including delayed ossification of the cervical vertebrae and sternebrae and the presence of extra ribs, were significantly increased in both the 50 and 250 ppm dose groups.

VII. Derivation Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Mild Adverse Effect Level

Because the most sensitive effect observed is developmental toxicity, a severe adverse effect, and since this effect is observed at or below the threshold for a less serious effect, no mild adverse effect level is recommended.

Reference Exposure Level for 6 hour exposure (protective against severe adverse effects): 0.1 ppm (370 μg/m^3)

Because of uncertainty in extrapolating from a repeated dose study to a one-hour concentration, for the reproductive/developmental endpoint we have chosen to use one day's exposure as the basis for the REL. Thus, the REL for EGEE is for a 6 hour exposure.

Study	Tinston *et al*., 1983; Doe, 1984
Study population	pregnant rats
Exposure method	inhalation 6 hours per day on days 6-15 of gestation
Critical effects	specific skeletal defects, including delayed ossification of the cervical vertebrae and sternebrae and extra ribs
LOAEL	50 ppm
NOAEL	10 ppm
Exposure duration	6 hours per day

LOAEL uncertainty factor	1
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Reference Exposure Level	0.1 ppm (0.37 mg/m³; 370 µg/m³)

Level Protective Against Life-threatening Effects

Mice were exposed to concentrations of 1,130-6,000 ppm EGEE for a single 7-hour exposure (Werner *et al*., 1943). Mortality during and up to 3 weeks following exposure was recorded.

The following data were used for benchmark calculation:

	EGEE concentration (ppm)						
7-hour data	1,130	1,580	1,740	1,830	2,210	2,800	5,500
1-hour equivalent	2,990	4,180	4,604	4,842	5,847	7,408	14,552
Mortality	2/16	4/16	6/14	9/16	11/16	15/16	16/16

A benchmark dose approach employed a log-normal probit analysis (Crump, 1983) of 7-hour mouse lethality data from Werner *et al*. (1943). The 7-hour exposure concentrations were extrapolated to 1-hour exposure equivalents using the equation $C^n * T = K$, where n = 2. From the 1-hour data, the concentration associated with a 5% incidence of lethality (ED_{05}) was 3,307 ppm; the lower confidence limit (LCL) on this concentration [the BC_{05}] was 2,223 ppm. An uncertainty factor (UF) of 30 was applied to the BC_{05} of 2,223 ppm (3 to account for interspecies variability and 10 for interindividual human variation).

$$\text{level protective against life-threatening effects} = BC_{05}/(UF)$$

The final level protective against life-threatening effects for EGEE is therefore 74 ppm (270 mg/m³). The maximum likelihood estimates (MLE) and 95% lower confidence limits (LCL) for the 1% and 5% response rates are indicated below. Refer to section IX of this toxicity summary for the graphic representation of benchmark dose derivation.

Comparison of benchmark concentrations (1% vs 5%)

Response rate	MLE (ppm)	95% LCL (ppm)
1%	2,766	1,635
5%	3,307	2,223

VIII. References

(ACGIH) American Conference of Governmental Industrial Hygienists. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th ed. Cincinnati (OH): ACGIH; 1991. p. 564-566.

(AIHA) American Industrial Hygiene Association. Odor thresholds for chemicals with established occupational health standards. Akron (OH): AIHA; 1989. p. 18.

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